YOUR GUIDE TO

THE SUBTILIS PATCH

(BBI transdermal system)

DESIGN

SPECS, VISUAL MODELS, CONSIDERATIONS

DESIGN SPECIFICATIONS

This section is dedicated to show how the Device team came up with the transdermal patch design, what it looks like, its parts and corresponding functions, and other design considerations. There are two patch designs included in this section: a simpler version used for laboratory testing and a more sophisticated and ergonomic design for future manufacturing of the patch.

MAIN IDEA

The main purpose of this transdermal patch system is to deliver radio-protective peptides (Bowman Birk Inhibitor (BBI)) produced by bacteria (B. subtilis) into the skin mainly by passive diffusion. What makes this patch different from the existing ones in the market is that the peptides are created in real time by bacteria living in the patch reservoir. Now, the Device team has to design a system that will keep the bacteria alive and to ensure the peptides are administered diffused to the patient in right dosages from the patch, all the way through the bloodstream.

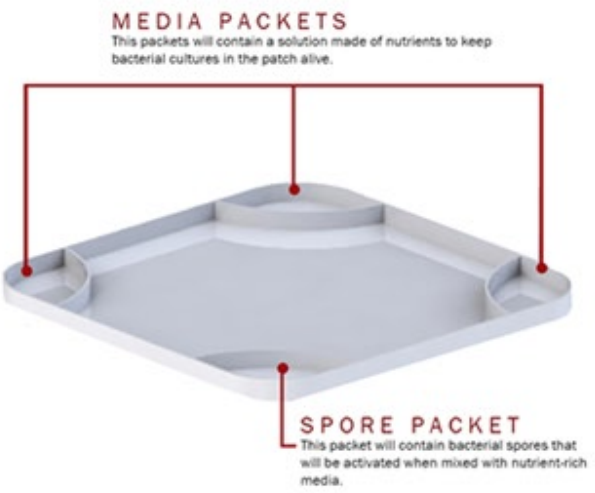
The patch would contain a backing layer that will protect the contents from external factors and contamination, a drug reservoir containing bacteria and media, a size and rate controlling membrane that will let peptides through while holding bacteria back, and an adhesive layer that will stick to skin for at least 7 days. The adhesive layer is protected to maintain its adhesion by a release liner.

This patch is designed to stay on the skin for a long period of time to accommodate an astronaut's way of life in space. The type of materials used and why those are chosen for this patch are listed under Materials section below.

PACKET IDEA

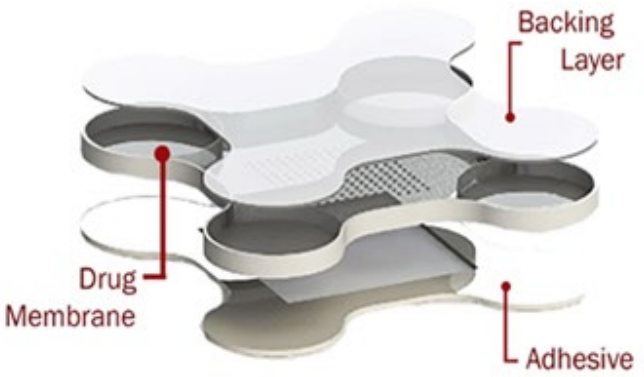
Compared to existing patches, this TDDS patch will have integrated packets on each corner, which will contain extra media and bacterial spores. These packets are meant to be squeezed or popped to be released into the middle compartment of the patch. The spore packet will be broken first to mix with media and transform into active state. The media packets are popped when the nutrients in the middle section run out. The following model shows the simpler design of the patch for testing purposes.

DESIGN SPECIFICATIONS



SOLIDWORKS

The following model shows a more sophisticated design of the patch. This design is meant to be more ergonomic. This means that it better accommodates stretching, and stresses and strains due to patient's movement compared to a square patch.



DIMENSIONS

The dimension of the simpler version (square patch) is **7 cm by 7 cm by 0.29 cm.** The patch will hold 10 mL of media in the main compartment and 1 mL in each pocket for a total of 14 mL of holding capacity.

For mice testing, the Device team created a patch that is 1 cm by 1 cm by 0.2 cm, which has a holding capacity of 0.2 mL.

DESIGN CONSIDERATIONS

QUALITY AND SAFETY CONSIDERATIONS

I. Maintain adequate physical stability and physical integrity of the transdermal system during storage and application – MATERIAL TESTING, MANUFACTURING

II. Minimize local skin reactions -- CHARACTERISTICS OF TTDS

III. Assure good adhesion and cohesion properties – CHARACTERISTICS OF TTDS

IV. Minimize risk of detachment during application

V. Minimize variability of skin adhesion and cold flow

VI. Deliver the required dose of drug into the patient – MODELLING

VII. Minimize the excess amount of drug remaining in the transdermal system after application – MODELLING

VIII. Minimize variability of drug absorption (cell membranes, other permeable factors in skin) -- MODELLING

MATERIALS

PRODUCTS, MATERIAL TESTING

MATERIALS

The patch is comprised of four major components. This includes the backing layer, drug membrane,adhesives, and the release liner. The material used are as follows. 3M provided the team with materials for the patch layers, while Dow Corning provided the team with adhesive samples.

PRODUCT

1

BACKING LAYER

3M CoTran™ 9722 Backing Polyethylene Monolayer Film

Use: Provides structural support, contains the bacteria and media and protects the middle adhesive layer from the environment
Type of material: Polyethylene
Advantages: Out of the three films 3M offers, the qualities that we thought would be beneficial are:
a) Elongation = for movement of patient, has to 600% elongation, highest of the three,
b) MVTR = this has the lowest amount out of all 3. This material is also translucent, breathable, printable, can be directly laminated to adhesives, heat sealable (PE), and designed to resist excipient and drug uptake

2

DRUG MEMBRANE

3M CoTran™ 9728 Ethylene Vinyl Acetate Membrane

Use: Rate controlling membrane controls drug diffusion into the adjacent adhesive layer and therefore is the rate-limiting step in the diffusion process.
Type of material: Ethyl vinyl acetate (EVA)
Advantages: The percentage of VA can be manipulated. Higher VA percentage means higher permeability and higher polarity. We would need these two factors for our patch to work. Maximum VA is 60% by weight (or else glass transition temperature will increase).

3

ADHESIVE

Dow Corning BIO-PSA Silicone-based Adhesive 7-4201

Use: Keeps the patch on the skin for a period of time, serves as the filler between the patch and skin interface to increase diffusion, constant delivery and absorption of drug.
Type of material: Silicone-based, pressure sensitive adhesive
Advantages: High oxygen/gas permeability, low pain upon removal to sensitive skin, can be customized to improve chemical compatibility and stability with cationic drugs, and increased diffusivity.

4

RELEASE LINER

3M Scotchpak 9755 Fluoropolymer Coated Polyester Film

Use: Needs to be chemically inert with drug penetration, penetration enhancer and water
Type of material: Fluoropolymer
Advantages: Good for release with silicon skin contact adhesives, acrylate, PIB and rubber based PSA and has excellent chemical stability

MANUFACTURING

COST ANALYSIS,
SMALL AND LARGE SCALE PRODUCTION,
STORAGE

COST - ANALYSIS

This section lists the different economic factors that the team had considered since the beginning of this research. A tentative amount of production once the patch is approved to be sold in the market is also considered in this analysis. This amount is then compared to costs of existing practices related to protection on Earth and in space. This section lists the different economic factors that the team had considered since the beginning of this research. A tentative amount of production once the patch is approved to be sold in the market is also considered in this analysis. This amount is then compared to costs of existing practices related to protection on Earth and in space.

EXPENDITURES

MONETARY

i) investment requirements

ii) grants, funding, scholarships or studentships

iii) sponsorships: these came from contacting external businesses as well

iv) fundraising: this was done when external business had generously donated some of their services to iGEM for raffles

v) operating costs

vi) laboratory equipment (reusable and non-reusable)

PERSONNEL

i) instructors

ii)ethics application and approval

iii) training of all people involved on the right protocols in the lab, safety and hazard trainings

iv) knowledge, morale, and employee retention

v) health and safety regulations and policy applications

vi) absenteeism of employees

PRODUCTION

i) re-tooling

ii) efficiency: in terms of time, a patch is manually created
(1)Materials

iii) equipment
(1)Foothills campus machine shop
(2)3D printed prototypes

ENVIRONMENT

xi) toxic emissions, waste management
costs, legal liability, fines
(1) chemical and biohazard waste disposal costs

CURRENT PRACTICES FOR RADIOPROTECTION

From the information gathered as listed below, radioprotection is indeed a need that must be fulfilled. As a summary, the Canadian government's budget for radiation protection in the medical field is estimated to be $13M for the year 2016 – 2017. NASA, on the other hand, is investing around $50M+ for research and development of radiation protection for astronauts in space. These estimated budgets are divided in different areas and they are as follows.

ON EARTH

In medicine (in North America): [1]

1. Medical imaging and therapy professionals recognize the importance of keeping radiation doses as low as possible for themselves, medical staff, and their patients. It is a basic standard of practice in radiology.
    a. Equipment use: Personal protective equipment
    b. Shielding facilities
2. Conferences are held wherein members of the radiology community tackle issues of minimizing radiation exposure in the medical field and lessen risks to patients. (**5000 CDN** [2])
3. There are organizations and ongoing campaigns worldwide that help spread awareness of opportunities to lower radiation doses. (free of costs)
4. Accreditation programs have been established to accredit facilities and make sure that these adhere to guidelines, and maintain competence and high personnel qualifications.
5. Policies and practices in radiology had also been established to help combat this issue.
6. Technologists, doctors, nurses, and staff in radiology receive education in radiation safety and protection.

The Department of Health granted the authority to the Radiation Protection program "to inform and advise other government departments, international partners, and Canadians in general about the health risks associated with radiation, and inform Canadians of strategies to manage associated risks." [3]

The following budget and human resources are proposed to execute this program. These values are subject to change as government priorities might change.

Table 1: Budgetary Financial Resources for Program 2.6 (dollars)

2015-16 Main Estimates	2015-16 Planned Spending	2016-17 Planned Spending	2017-18 Planned Spending
20 282 587	20 282 587	13 097 382	12 829 033

CURRENT PRACTICES FOR RADIOPROTECTION

IN SPACE

There are many sources of radiation in space and these are some of the following [4]:

- the structure of the spacecraft,
- the materials used to construct the vehicle,
- the altitude and inclination of the spacecraft,
- the status of outer zone electron belts,
- the interplanetary proton flux,
- geomagnetic field conditions,
- solar cycle position, and
- extra-vehicular activity start time and duration

How are the astronauts protected from radiation exposure?

- Providing radiological support during missions.
  - Space control centres work closely with the environment centres to monitor and provide alerts and warnings about space weather conditions 24 hours a day.
- Projecting pre-flight and extra-vehicular activity (EVA) crew exposures
  - "In order to support mission planning, the Space Radiation Analysis Group maintains an extensive set of tools for estimating the exposure received by the crews of manned missions in Low Earth Orbit (LEO). This suite of tools includes time-resolved models of the Earth's magnetic field, maps of the radiation fluxes trapped in the geomagnetosphere, and trajectory translator/propagator algorithms."
- Evaluating radiological safety with respect to exposure to isotopes and radiation producing equipment carried on the spacecraft
- Maintaining comprehensive crew exposure modeling capability
  - state-of-the-art radiation transport codes and CAD-based geometry evaluation tools
- Providing radiation instruments to characterize and quantify the radiation environment inside and outside the spacecraft
  - Tissue Equivalent Proportional Counter (TEPC),
  - Charged Particle Directional Spectrometer (CPDS),
  - Radiation Area Monitor (RAM), and
  - Crew Passive Dosimeter (CPD)

Under development:

- Hydrogenated boron nitride nanotubes—known as hydrogenated BNNTs
- Building force fields
- Other radiation shielding

Snapshots from NASA's 2016 Budget Document (pdf) [5]:

BUDGET FOR INTERNATIONAL SPACE STATION RESEARCH

The Human Exploration and Operations Mission Directorate supports research which takes advantage of the unique environment of reduced gravity on the International Space Station (ISS). Human Explorations and Operations ISS Research is conducted in two broad categories: Exploration ISS Research and Non-Exploration ISS Research.

	Actual	Estimate	Request	Notional			
Budget Authority ($ millions)	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018	FY 2019	FY 2020
Exploration ISS Research	133	141	175	156	157	162	164
Non-Exploration ISS Research	155	148	185	169	170	171	171
Total	**289**	**290**	**360**	**325**	**327**	**333**	**335**
Percent of Non-Exploration to Total	54	51	51	52	52	51	51

The amounts included for FY 2014 reflect actual, FY 2015 thru FY 2020 are reflective of the NASA outyear planning.

FY 2016 Budget

	Actual	Enacted	Request	Notional			
Budget Authority (in $ millions)	**FY 2014**	**FY 2015**	**FY 2016**	**FY 2017**	**FY 2018**	**FY 2019**	**FY 2020**
Earth Systematic Missions (ESM) Research	12.1	--	**16.6**	18.8	18.8	24.0	24.2
Ocean Surface Topography Science Team (OSTST)	6.0	--	**6.2**	5.8	5.8	5.8	5.9
Earth Observations Systems (EOS) Research	33.1	--	**24.1**	22.9	20.9	18.7	18.8
Deep Space Climate Observatory	4.5	--	**2.9**	0.5	0.0	0.0	0.0
Stratospheric Aerosol and Gas Experiment III (Sage III)	22.6	--	**21.1**	4.8	3.9	4.6	4.6
Sustainable Land Imaging	30.0	--	**78.9**	134.6	174.4	179.9	147.3
Radiation Budget Instrument (RBI)	18.6	--	**45.3**	38.6	28.7	12.2	6.3
NASA-ISRO SAR	57.3	--	**74.0**	64.4	85.0	150.0	145.0
Earth from ISS	0.0	--	**2.3**	2.8	3.1	3.1	3.1
Total Solar Irradiance Sensor-2 (TSIS-2)	0.0	--	**1.0**	9.6	25.9	42.9	31.5
Earth Radiation Budget Science	0.0	--	**12.8**	14.0	13.7	13.6	13.8
Ozone Mapping and Profiler Suite Limb Sounder (OMPS-L)	7.4	--	**5.7**	2.2	0.3	0.0	0.0
Total Solar Irradiance Sensor-1 (TSIS-1)	0.0	--	**16.0**	21.0	13.5	4.0	3.0

	Actual	Enacted	Request	Notional			
Budget Authority (in $ millions)	**FY 2014**	**FY 2015**	**FY 2016**	**FY 2017**	**FY 2018**	**FY 2019**	**FY 2020**
Balloon Array for Radiation-belt Relativistic Electron Losses (BARREL)	1.5	--	**0.0**	0.0	0.0	0.0	0.0
LWS Space Environment Testbeds	0.6	--	**0.4**	0.4	0.0	0.0	0.0
LWS Science	18.2	--	**17.5**	17.5	25.5	30.5	29.5
LWS Program Management and Future Missions	5.9	--	**6.7**	6.9	7.8	15.3	26.8
Van Allen Probes (RBSP)	10.8	--	**15.5**	14.3	14.0	14.0	10.0
Solar Dynamics Observatory (SDO)	14.8	--	**9.5**	9.5	9.5	9.5	9.5
Total Budget	**51.7**	--	**49.7**	**48.7**	**56.9**	**69.4**	**75.9**

FY 2014 reflects funding amounts specified in the June 2014 Operating Plan per P.L. 113-76.

FY 2015 reflects only funding amounts specified in P.L. 113-235, the Consolidated and Further Continuing Appropriations Act, 2015.

METHODS OF PRODUCTION

SMALL SCALE

Objective:
The objective of prototyping is to create 18 working transdermal patches for the purpose of mice testing. There are 3 variations, consisting of 6 patches with no media, 6 patches with media containing BBI and 6 patches containing live bacteria.

Materials:

- Strips of release liner (5cm x 13.2 cm)
- Strips of EVA membrane (5cm x 13.2 cm)
- Square cut outs of backing layer
- BIO PSA adhesive
- Cylindrical metal bar
- Masking tape
- Scissors, marker, ruler
- Stopwatch
- Flat rigid plastic surface
- Iron and ironing board
- Syringe + needle

Procedures:
Preparation of the adhesive layer

a) Have the materials ready. Perform the process under the fume hood as the adhesives contain heptane. Heptane is flammable and create vapor trails that may cause fire.
b) Note that the coated side of the liner is where the adhesive will be applied. In case you cannot figure which one is the right side, grab a marker and try to write on both sides of the liner. If the ink stayed permanently on the liner, you wrote on the uncoated side. The side where the ink just slipped through would be the coated side. It would be recommended to write which side is which to avoid confusion.
c) Draw a horizontal line on one end of the release liners (1cm from the end) with a marker. This end will be taped to keep the liner in place when the adhesive is being applied.
d) Draw three 3cm x 3cm squares on the release liners. Make sure to leave ample amount of space between the squares. Draw 1cm x 1cm squares inside the initial squares.
e) Take all the materials under the fume hood. Tape the end release liner on the flat plastic surface.
f) Apply the adhesive on the line initially drawn. Apply a constant pea-size amount on the line.
g) Using the metal bar, spread the adhesive onto the liner. Spreading using a metal bar will form a thin film of adhesive on the liner.
h) Wait for about a minute before placing the EVA on the layer.
i) Carefully place the EVA membrane strip on the adhesive layer.
j) Lightly tap the membrane to stick. Eliminate air bubble by gently applying pressure to spread the adhesive evenly.
k) Wait for the adhesive to completely dry (1 hr - 3 hrs).
l) Cut out the squares.

SMALL SCALE

Method 1: Iron sealing method

1) **Heat sealing the patch**
   a) Set the iron to the heat sealing temperature that was previously determined. (Future directions: having a thermometer that would measure the exact temperature of the iron or material we are using to heat seal)
   b) Place the backing layer on top of the prepared adhesive-membrane layer.
   c) Carefully iron the sides of the layer. Avoid ironing parts of the 1cm x 1cm square centre drawn. This is where the nutrient rich media and bacteria will be stored.
   d) Also note that only use non-stick metal or materials when heat sealing. The layers used for these prototypes stick to metals such as stainless steels. (Future direction: apply a non-stick lubricant or Teflon-based coating on the metal heat sealer).
2) **Adding the media in**
   a) Obtain the required amount/volume of media to be stored in the patch using a syringe.
   b) Use the adhesive laminates following procedures from 1).
   c) Plug the iron in to preheat.
   d) Look through the adhesive laminate under a light source and pick out and most even area. Sketch the 1 x 1 cm square on the liner at the center of the area
   e) Trim the laminate to roughly 1.5 x 1.5 cm
f) Lay the laminate membrane-side up on the iron board, and the backing layer on top
g) Iron one side of the patch up to the sketch.
   i) To make the seal even and bubble free, when sealing, apply more pressure on the side of the iron that is touching the line.
   ii) Only use the edge of the iron in sealing the patch. Press the iron down and after each time, move the iron away from the line to the edge of the patch by lifting it. The seal should look clearer than the center. If not, then the iron is not hot enough.
   iii) Redo using a different side of the iron until it's clear.
h) Seal the other 3 edges. Repeat the process for another 2 patches.
i) Remove the first patch from the iron board.
j) Hold the patch backing layer side facing you. Bend it slightly so the backing folds towards you. The backing at the center (not sealed) should bend and separate from the membrane, creating a thin pocket running diagonally from the top corner to the bottom corner.
k) Fill the syringe with water, use the needle to poke a hole at the top corner of the patch, make sure the needle did not poke anywhere else and the needle is in deeper than half of the patch.
l) Inject the water slowly, keep a bend in the patch so we have a pocket, fill it from the bottom corner, and tilt the needle and the patch to get the other 2 corners, then fill it nearly to the top corner. A good volume should be 0.06 - 0.08 mL
m) Remove the needle straight out, a drop of water may leak out, dry it lightly with paper towel, don't push on it.
n) Lay it on the iron board. Make sure there's no water droplet visible. If there is, dry it gently with a paper towel, then iron on the hole for about 1-2 seconds
o) Press on the patch slightly to see if there's still any leaks, if yes, dry the droplet of water with paper towel and re-iron the corner until there's no more leaks.
p) Now the patch is done, trim the sealed sides with scissors to approximately half of the original side dimensions. Round off the sharp corners.

SMALL SCALE

Method 2: Thermoforming

Mold compartments
The molds and brand were made by the machine shop with specifications to create 1 cm x 1 cm x 0.2 cm patches. All parts, specifically the metals, are coated with Teflon for non-stick properties as the polymer layers are found to stick to metals when heated.

- Aluminum 1 cm x 1cm x 0.2cm negative well mold
- Aluminum 1cm x 1cm x 0.2cm positive mold
- Brass square brand with a hollow 1cm x 1cm x 0.2cm center

1) **Adding the media in**
   a) Heat a 5 cm x 5 cm backing layer up until it is malleable.
   b) Place the backing layer matte side down on the negative mold.
   c) Press the positive mold onto the negative mold with the backing layer in between.
   d) Trim the excess materials around the edges and remove the positive mold
   e) Pipette 0.2 mL of media into the wells.
2) **Heat sealing the patch**
   a) Heat the brand to the appropriate temperature (1100C)
   b) Align the membrane with adhesive and liner on top of the media filled-backing layer in the negative mould.
   c) Press the brand on top of the layers and hold for 5 seconds
   d) Repeat step 3 until the backing layer is completely sealed to the membrane

Storage

i. The whole patch system with the media in are stored collectively in a clean, disinfected, and dry container. It is recommended to store the patches in room temperature environment
as intense heat may cause the materials to melt and cold temperatures can alter some properties of the adhesive and/or polymers.
ii. Since the patches contain volume of media, they are sensitive to increased pressure changes. It must be ensured that the patches are not placed in tight places or containers or where there is potential for being squished/flattened.

METHODS OF PRODUCTION

LARGE SCALE

This process will be potentially used to manufacture in bigger scale for astronauts' use for their missions. The following is an excerpt that was from 3M's email to the team when asked about manufacturing of the patch:

Heat sealing for thermal forming procedure
The temperature, pressure and dwell time are the important factors for sealing the membrane to the backing. It really depends on the equipment – for our small single well sealer, it would be recommended to reduce the temperature to 2500F, with a 40 psi pressure and 1 sec dwell time to make sure that the liner didn't warp. However, for multiple well sealer, the temperature has to be increased to 3000F and the pressure to 50 psi to get a good seal. Some initial trials are needed to be done to get the right parameters for the equipment to be used.

Recommended procedure:

1)Coat adhesive onto the liner.
2) Laminate the membrane to the liner through a low pressure nip roller.
3) Heat seal the backing to the lamination (on the membrane side) by placing the materials to be sealed onto a well type receiving fixture with silicone sealing gaskets and using a platen type seal plate above.

Permeability
With regards to the membrane permeability – permeability increases with an increase in %vinyl acetate in the copolymer or with a thinner material. Since 9716 and 9728 both have the highest vinyl acetate that 3M offers at 18.5%, the difference will be in the thickness with 9716 having a slower transmission rate due to its thickness of 4 mil versus 2 mil for 9728. If membrane did not work for the compound of interest, the other thing to consider is a microporous membrane. (End of excerpt)

Integration of packets
These packets will also be added as part of the mould for thermal forming. The barrier that will separate packet contents from the middle media compartment will be made of thin, non-permeable membrane. This membrane must be designed or customized such that when squeezed, it would allow the passage of the contents out of the packets. The spore packet barrier will be the easiest to break, followed by the media packets.

Storage

i. The patches made will be stored in a plastic-aluminum pouches under room temperature until use.
ii. Store the patches away from children or any source of fire. As long as the media are inaccessible to bacterial spores, there is no known expiration time for this patch.
iii. Since the patches contain packets, they are sensitive to increased pressure changes. It must be ensured that the patches are not placed in tight places or containers or where there is potential for being squished/flattened.

USAGE

APPLICATION, REMOVAL, TROUBLESHOOTING

WHAT OUR PATCH IS

TYPE

Our patch is a transdermal drug delivery system consisting of **membrane controlled reservoir.** Unlike the currently existing patches, this patch contains bacterial cultures that produce peptides. These peptides are contained in the reservoir and delivered to the skin through a microporous membrane and adhesive laminate. The design considerations, and thoughts with regards to the making of the patch are stated in the sections above.

These patches **should not be altered** in any way possible as the main goal is to maintain an optimal growth environment for bacteria in the patch. All the guidelines in applying and removal of the patch, and troubleshooting problems with the TDDS are listed on the next pages..

APPLICATION

1. Before application, it must be ensured that the skin area of application is clean, dry, hairless, and non-irritated. Disinfect the area using alcohol or disinfecting wipes or wash with soap and water.
    a. The patch should not be applied to areas where there is tight clothing or exposed to heat.
    b. Avoid using any topical cream or powder on the skin as these may affect the adhesive properties of the patch.
    c. Do not apply the patch to areas of skin with abrasions or scars as these may interfere with diffusion.
2. Carefully remove the patch from its storage area. The patch is stored in an aluminum pouch. Avoid using scissors or any sharp objects in opening the pouch. If need be, make sure that the patch is not anywhere near the location of cutting. Puncturing any part of the patch may lead leakage of harmful bacteria or contamination.
3. Only use one patch at a time unless instructed otherwise.
4. Write the date and time of the application of patch on the backing layer using a fine tip permanent marker. This would help in remembering when to remove the patch. Other methods, such as having a calendar or something to help the user to monitor patch time will be helpful.
5. To use the patch, the user must peel off the release liner on the adhesive layer and apply it onto the skin firmly. Slight pressure must applied to the patch in about 10 minutes in order to activate the adhesive. The more pressure applied to it, the stickier it gets. Make sure that the patch is fully sealed to the skin such that no water or air can get in.
6. Once on the skin, the first packet can be popped. This packet has a letter "S" written on it. The patch can be activated by popping the pocket containing the sporulated bacteria in water.
    a. Upon contact with the supply of rich media in the main compartment, the bacteria spores turn into their active state. Once they can then begin to secrete our peptide, BBI, the solution will turn pink. B. subtilis will be contained from contacting the patient by a semipermeable membrane. The membrane has pores large enough to allow the passage of the peptides, but small enough such that the bacteria will not be able to pass.
7. After sometime, the bacteria will use up all the media. To continuously supply them with media, pop one of the packets with letter "M" written on. This packets must be popped in 1 day time interval.
8. Once all the media have been used up, the bacteria can no longer produce BBI and will proceed to death phase. The patch must be removed from the skin at this point. Refer removal procedure.
9. Rotate sites for every application.

REMOVAL

1.Peel off one corner and remove the patch completely from the skin carefully. Peel off in the direction of hair growth to lessen pain from removal. Adhesive residues can be removed using baby oil.

2. Dispose the used patch in the garbage can.

TROUBLESHOOTING

PROBLEMS BEFORE APPLICATION

a) **If the adhesive does not stick:**

i) As an initial solution, apply more pressure to the adhesive by pressing the sides of the patch to stick better. Note that the adhesive is pressure-sensitive, such that the more pressure applied to it, the stickier it gets.

ii) It must be ensured that the area of application is free from oil, dirt, or any chemicals, such as topical creams. Follow the initial steps as mentioned above in the 'Application of the Patch' section on how to do this. These agents will affect the adhesive properties of the patch. After doing so, apply a fresh patch on the recommended skin area after completely cleaning and disinfecting the skin.

iii) If the cause of loss of adhesion is not the presence of skin agents, replace and apply the patch on a different site following the protocols for application.

b) **If the patch leaks media:**

i) This may happen due to accidental poking of the patch with a sharp object when opening the package, bursting of packets when stored, or a manufacturing defect.

ii) Assess the patch. If one of the media packets was damaged, squeeze all the media out of the packet and dry the patch with cloth. Once dried, the patch can be applied to the recommended area following the protocols for patch application. The lifetime of the patch will therefore decrease as a result of loss of media.

iii) If it was the middle compartment of the patch that was damaged, discard the patch and apply a fresh one.

iv) If it was the spore packet that was damaged, refer to 1.c).

c) **If the spore packet was damaged:**

i) Spores are somehow resistant to heat, pressure, or chemicals, which makes it ideal for storage. However, this may pose dangerous side effects if not given attention to when spilled or accidentally dispersed. To solve this problem, firstly, disinfect the spill area with bleach. All clothing or materials around the area of spill or splash must be collected to be autoclaved.

d) **If the wrong packet was popped:**

i) This may happen before patch application. If one of the media packet was popped first instead of the spore packet, it will result to richer media in the middle compartment. More media means more nutrients for the bacteria to consume. If this happens, simply pop the bacterial spore packet onto the middle compartment next.

TROUBLESHOOTING

PROBLEMS AFTER APPLICATION

a) **If the adhesive does not stick:**
   i) This may happen due to air or water leaking into the adhesive layer during bathing, accidental liquid spills, swimming, or rigorous movements. Bathing or swimming may be limited in space, but air leakage might be a problem.
   ii) If detachment occurs, apply the extra adhesive strips (included in the package, not in each pouch) on the sides of the patch.

b) **If the patch leaks media:**
   i) This may happen due to the activities of the user, exposure of the patch to heat, etc.
   ii) Assess the patch. If the media were coming from one of the packets, disinfect the surrounding skin area where it leaked using wipes or rubbing alcohol. Avoid wetting the inner sides of the patch as the adhesives may be affected. Empty the media packet completely by squeezing the media onto the middle compartment. If the damage was substantial, squeeze all the media out of the packet and dry the patch with cloth.
   iii) If the middle compartment was damaged, find the source of leak and cover it with a small piece of adhesive laminate from the package. Carefully peel off the patch from the skin and dispose it in its designated place. Disinfect the skin area using wipes or rubbing alcohol.

c) **If there are adhesive residues left on the skin after patch removal:**
   i) Apply an amount of baby oil in the area where there is residue. Wipe it off using a clean cloth or paper towel.

PROBLEMS WHEN ON SKIN

a) **If there is irritation that appeared in the area of application:**
   i) Irritation can be in the form of redness or rashes due to removal of oil in the stratum corneum, allergic reactions from the components of the patch, effect of prevented water evaporation and/or sweat, irritant effects of topical cream/chemical residues, and friction between surrounding skin and skin under the patch.
   ii) If irritation occurs, discontinue use and seek medical help as soon as possible.

REFERENCES

[1](ACR), R. (2016). Managing medical radiation exposure to patients. Radiologyinfo.org. Retrieved 1 October 2016, from http://www.radiologyinfo.org/en/info.cfm?pg=safety-hiw_15

[2]Report on Annual Expenditures for Travel, Hospitality and Conferences - 2014-2015 - Canadian Nuclear Safety Commission. (2014). Nuclearsafety.gc.ca. Retrieved 1 October 2016, from http://nuclearsafety.gc.ca/eng/resources/publications/reports/annual-expenditures-for-travel-hospitality-and-conferences/raethc-2014-2015.cfm

[3]Health Canada 2015-16 Report on Plans and Priorities. (2016). Hc-sc.gc.ca. Retrieved 1 October 2016, from http://www.hc-sc.gc.ca/ahc-asc/performance/estim-previs/plans-prior/2015-2016/report-rapport-eng.php#p2.6

[4]How do we protect the astronauts from space radiation?. National Aeronautics and Space Administration. Retrieved 1 October 2016, from https://srag.jsc.nasa.gov/spaceradiation/how/how.cfm

[5]Frazier, S. (2015). How to Protect Astronauts from Space Radiation on Mars. NASA. Retrieved 1 October 2016, from http://www.nasa.gov/feature/goddard/real-martians-how-to-protect-astronauts-from-space-radiation-on-mars